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Biochemical and Genetic Studies of Epstein-Barr Virus Latent Membrane Protein 2

Most cancers result from a multistep process. Viruses can play a significant role in converting a normal cell to a cancer cell. The study of oncogenic viruses has uncovered important aspects of how they control cell growth and key points in cell growth control which are also important in malignancies not caused by viruses. Epstein-Barr Virus (EBV) is an etiological factor in some human lymphomas and carcinomas. Recent experiments have begun to identify the mechanisms by which Epstein-Barr (EBV) alters cell growth. The proposed research will apply molecular genetic and molecular biologic techniques to explore the role of a newly defined EBV gene in lymphocyte growth transformation. Understanding EBV transformation may provide insight for the development of novel therapeutics for EBV related malignancies.

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The Role of Aldehyde Dehydrogenase in Cyclophosphamide Resistance

Treatment of cancer with chemotherapeutic drugs is based on the fact that cancer cells are generally more sensitive to the toxic effects of these drugs than normal cells. However, significant toxicity to normal cells usually also occurs, and this host toxicity limits the drug dosage that can be given. Therapeutic failure occurs when the malignant cells are no more sensitive to the drug than normal cells, and therefore cannot be eradicated with a drug dose that the patient can tolerate. This phenomenon, termed "drug resistance," can be due to several factors, including metabolism of the drug in resistant cells to a chemical form which is no longer toxic. Metabolic detoxification may play a role in resistance of cancer cells to cyclophosphamide (CPA), a drug used to treat leukemias, lymphomas, multiple myeloma, and some solid tumors. The enzyme aldehyde dehydrogenase (ALDH), which is involved in alcohol metabolism, also has the ability to break down aldophosphamide, a key metabolite of CPA. Although ALDH has been found to be increased in cells resistant to CPA, it is not yet clear if this change is the only factor in CPA resistance, or how much effect the increased ALDH alone has on sensitivity of these cells to the drug. This problem has been resolved directly and without ambiguity by transferring previously isolated ALDH genes into cultured cell lines which do not normally express these isoenzymes, and comparing their sensitivity to CPA to that of the original cell lines. The objective of this project is to utilize these transgenic model systems to extend our understanding of the role of ALDH in cellular resistance to CPA and to aid in identification of nontoxic compounds which reverse CPA resistance by selectively inhibiting ALDH isoenzymes. A second goal is to determine whether these natural protective enzymes may be increased in normal cells by growth factors that are normally present in human serum, and by other inducers as well.